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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,574	07/20/2001	Frank A. Skraly	MBX 039	2982

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,574	SKRALY ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on June 5, 2006, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing at the end of this Action.

Claims 1-4 and 6-10 are pending and are under consideration.

Response to Arguments

Applicant's arguments filed on June 5, 2006, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Rejection of claims 1-4 and 6-10 under 35 USC 112, 1st paragraph for lacking written description has been withdrawn for the following reasons.

Applicants argue that "[s]ince the enzymes were known, their substrate specificity known, the nucleotide sequences encoding the enzymes known and production of PHAs in genetically engineered bacteria and plants well established", the claims comply with the written description requirement (Appeal Brief, page 19). Applicants also argue that the "enzymes utilized in the method and system defined by the claims are well-known and exist within well-defined classes of proteins (Appeal Brief, page 9, 1st full paragraph) and cite art (with publications before that of the priority application of the instant application) to "demonstrate that the genes and enzymes can be obtained from a number of organisms and that sequence information for both aldehyde dehydrogenase and diol oxidoreductase were well known in the art as of the priority date of this application" (Appeal Brief, page 12, 2nd paragraph) and to demonstrate that "[i]t was also well known that a number of different organisms have the cellular machinery to produce polyhydroxyalkanoates, either endogenously, or through genetic engineering" (Appeal Brief, page 13, 1st full paragraph).

Rejection of claims 1-4 and 6-10 under 35 USC 112, 1st paragraph for lacking enablement has been withdrawn for the following reasons.

Applicants argue that the "prior art disclose organisms that can be genetically engineered to produce PHAs" (Appeal Brief page 23, 2nd paragraph), "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any

combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief, pages 24-25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skraly, Madison et al., and BRENDA database.

Claims 1-4 and 6-10 are drawn to a method of producing PHAs by providing an *E. coli*, which expresses acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase,

acetoacetyl-CoA reductase or PHA synthase, wherein said bacteria is genetically engineered to express polynucleotides that encode a diol oxidoreductase or aldehyde dehydrogenase, wherein the enzyme expressed by the bacteria convert 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol into 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate or 2-hydroxypropionate monomers, respectively, and producing PHAs having a weigh-average molecular weight of at least 300,000 Da.

Skraly (*Polyhydroxyalkanoates Produced by Recombinant E. coli*, Poster at Engineering Foundation Conference: Metabolic Engineering, 1998 – form PTO-892) discloses a recombinant *E. coli which* expresses PHA synthase and *K. pneumoniae* diol oxidoreductase (page 9), wherein a diol, 1,3-propanediol, is oxidized to its corresponding aldehyde and then converted to its corresponding hydroxyalkanoate monomer via an aldehyde dehydrogenase and CoA transferase (page 8). *E. coli* produces aldehyde dehydrogenase naturally (see "aldehyde dehydrogenase"). Skraly discloses a method of producing novel PHAs using such recombinant *E. coli*, wherein PHAs are generated using inexpensive PHA precursors, such as polyols:1,2-propanediol (converted to 2-hydroxypropionate), 1,4-butanediol (converted to 4-hydroxybutyrate) and 1,5-butanediol (converted to 5-hydroxyvalerate) (pages 1, 6-7 and 9). With these teachings at hand, one having ordinary skill in the art would have concluded to design recombinant *E. coli* systems expressing enzymes necessary for PHA synthesis and diol oxidoreductases, in order to convert inexpensive carbons sources such as diols into novel PHA monomers.

As applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief, pages 24-25). Madison et al. (Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. Microbiol Mol Biol Rev. 1999 Mar;63(1):21-53 – form PTO-1449) is cited here to provide evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Madison et al. also teaches that the molecular mass of PHAs produced varies from 50,000 to 1,000,000 Da and bacterially produced PHAs have a high molecular mass (page 22).

The difference between the reference of Skraly and the instant invention is that the reference of Skraly does not explicitly teach a method of producing PHA from the recited diols of claims 2-7 using a diol oxidoreductase.

However, BRENDA database ("EC 1.1.1.202"– form PTO-892) discloses several diol reductases that oxidize diols and that have been cloned and expressed in *E. coli,* including the *K. pneumoniae* diol oxidoreductase used by Skraly and the instant invention. Further, BRENDA database discloses a 1,3-propanediol dehydrogenase isolated from C. *freundii* which oxidizes several diols, 1,3-propanediol, 1,2-propanediol and 1,4-butanediol, and its expression in *E. coli* (pages 2-3). This enzyme has been cloned and expressed in *E. coli* (pages 10 and 12) as evidenced by Daniel et al. (J

Bacteriol. 1995 Apr;177(8):2151-6 - form PTO-892). Daniel et al. also teaches that said enzyme oxidizes all primary, secondary and tertiary alcohols (Daniel et al. on page 5152). Even though 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol are not explicitly listed as one of the substrates, since the enzyme is able to oxidize primary alcohols and diols containing two primary alcohols, one having ordinary skill in the art would have reasonably expect for the enzymes to oxidize 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol. Also, one having ordinary skill in the art would have used other diol reductases of BRENDA database to oxidize the recited diols.

Therefore, combining the teachings of Skraly and BRENDA database, it would have been obvious to one having ordinary skill in the art to produce PHAs using the method of Skraly by converting the recited diols by using a recombinant *E. coli* that expresses acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase as taught by Madison et al, and that has been genetically engineered to express a diol oxidoreductase, such as the *K. pneumoniae* diol oxidoreductase used in Skraly or other diol oxidorecutases known in the art, such as those taught by BRENDA database. One of ordinary skill in the art would have been motivated to produce PHA using 1,3-propanediol or the recited diols in order to produce novel PHAs using inexpensive starting materials. One of ordinary skill in the art would have had a reasonable expectation of success since Skraly teaches a method of producing PHAs from diols using a diol oxidoreductase/aldehyde dehydrogenase and BRENDA database teaches several diol oxidoreductases that have been cloned into *E. coli* that have a wide range in substrate specificity. One having ordinary skill in the art

would have had a reasonable expectation of success since production of PHAs in recombinant organism, such as *E. coli*, expressing enzymes necessary for PHA production is well known in the art and diol oxidoreductases, which have been cloned and expressed in *E. coli*, having a wide range of substrate specificity are well known in the art.

Therefore, the above references render claims 1-4 and 6-10 *prima facie* obvious to one of ordinary skill in the art.

None of the claims are allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

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